What’s New in Pain and Palliative Care Medications?

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Disclosure

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Why ARE you here?

Learning Objectives

- List new drugs approved by the FDA that may be used by hospice and palliative care patients.
- Describe the approved indications, unapproved uses of the medication, common adverse effects and drug interactions for each drug.
- Describe the burden-to-benefit ratio and the role of the medication in caring for patients with advanced illness.
- Analyze important drug alerts released by the FDA (Drug Safety Alerts) and their relevance to drug therapies commonly used in hospice and palliative care patients.
IONSYS

- Used for the management of acute pain, in hospitalized patients.
- Patient-controlled iontophoretic transdermal system providing on-demand systemic delivery of fentanyl, an opioid agonist, for up to 24 hours or a maximum of 80 doses, whichever comes first.
- 40 mcg/activation; max of 6 doses/hour

**Indications and Limitations**

- Indication – For the short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital.
- Limitations
  - Only for patients alert enough and have adequate cognitive ability to understand directions for use.
  - Not for home use; only for use in hospital. DC IONSYS before discharge.
  - For use after patients have been titrated to an acceptable level of analgesia using alternate opioid analgesics.
IONSYS

- Do not use more than one IONSYS at a time
- Apply to intact, non-irritated, and non-irradiated skin on the chest or upper outer arm
- May be used for a maximum of 72 hours of therapy for acute postoperative pain, with each subsequent IONSYS applied to a different site
- To initiate administration of IONSYS, the patient must press and release the button twice within 3 seconds
- One single audible beep indicates the start of delivery of each dose; green light blinks rapidly
  - When the 10 minute dose is complete the green light blinks at a slower rate, and displays number of doses delivered
Disposal of IONSYS

To dispose of a used IONSYS:
1. With gloves on, pull the red tab to separate the red bottom housing containing fentanyl from IONSYS (see Figure 7a).
2. Fold the red housing in half with the sticky side facing in (see Figure 7b).
3. Dispose of the folded red housing containing the residual fentanyl per the institution’s procedures for disposal of Schedule II drugs or by flushing it down the toilet.
4. Hold down dosing button until the display goes blank and then dispose of the remaining part of IONSYS containing electronics in waste designated for batteries.


Iontophoresis

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive, rapid analgesia</td>
<td>Not appropriate for patients with skin disorders or injuries that prevent application</td>
</tr>
<tr>
<td>Convenient, small size, no required cables or pump</td>
<td>Individualization of dosing limited to frequency of dosing</td>
</tr>
<tr>
<td>No programming by hospital staff required</td>
<td></td>
</tr>
<tr>
<td>No first-pass GI effect</td>
<td></td>
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<tr>
<td>Limited time and resources required for administration</td>
<td></td>
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<tr>
<td>Patient-controlled</td>
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</tbody>
</table>
FDA Definitions of Abuse-Deterrent Formulations

- **Physical/chemical barriers**
  - Physical barriers prevent chewing, crushing, cutting, grating or grinding.
  - Chemical barriers can resist extraction of the opioid using common solvents such as water, alcohol, or other organic solvents.

- **Agonist/antagonist combinations**
  - Opioid antagonist (e.g., naloxone) can interfere with, reduce or defeat the euphoria associated with abuse.
  - Antagonist can be sequestered and released only upon manipulation of the product.

Practical Pain Management, August 2014, p. 15

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FDA Definitions of Abuse-Deterrent Formulations

- **Aversion**
  - Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used.

- **Delivery system (including depot injectable formulations and implants)**
  - Certain drug-release designs or the method of drug delivery can offer resistance to abuse.
  - Sustained-release depot injectable formulations administered as IM or SC implants can be more difficult to manipulate.

Practical Pain Management, August 2014, p. 15
FDA Definitions of Abuse-Deterrent Formulations

- Prodrug
  - A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for IV or intranasal routes of abuse
- Combination
  - Two or more of the above methods can be combined to deter abuse.

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Targiniq ER
(Tar-gin-iq, like be-gin)

- Oxycodone/naloxone, controlled release
- For management of chronic pain- severe enough to require daily, around-the-clock, long-term opioid treatment, in whom other treatment methods were unsuccessful
- NOT a “prn” analgesic
- Abuse-deterrent
  - When crushed and snorted, or crushed, dissolved and injected – naloxone blocks euphoric effects of oxycodone
  - Taking excessive doses orally still may occur
**Targiniq ER**

- Available as:
  - Supplied as (oxycodone/naloxone):
    - 10 mg/5 mg (starting dose, 1 tab q12h)
    - 20 mg/10 mg (can only use if meets FDA definition of opioid tolerance [TDD OME 60 mg/day x 1 week])
    - 40 mg/20 mg

- One tablet every 12 hours
  - Maximum approved dose if 40 mg/20 mg po q12h

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**Xartemis XR**

- Indicated for the management of **acute pain** severe enough to require opioid treatment and for which alternative treatment options are inadequate
- Bilayer combination – IR and ER oxycodone plus acetaminophen for acute pain in patients > 18 years old
- One tablet = 7.5 mg oxycodone/325 mg acetaminophen
- Dose: 2 tablets every 12 hours
- 3.75 mg oxy/325 mg aceta are immediate release
- 11.25 mg oxy/325 mg aceta are extended release over 12 hours

Xartemis XR Tampering Studies (vs. IR OC/APAP)

- In vitro particle size reduction
  - Preconditioning: Open flame heating, crisping, freezing, microwaving
  - Particle size reduction (hammer, pill crusher, mortar and pestle, knife, 2 spoons, utility knife, blender, coffee mill and coffee grinder)
- In vitro dissolution studies
  - Solvents: Water, vinegar, 3% sodium bicarbonate, 100-proof vodka, 70% isopropyl alcohol, mineral spirits
  - Intact and mechanically disrupted (after mortar and pestle) dosage forms
    - At room temperature and near boiling point of the solvent
- In vitro assessment of feasibility of insufflation
  - Xartemis XR formed a clumpy, solid mass vs. IR OC/APAP formed a thin, fluid film
- In vitro assessment of feasibility of injection
  - Extent to which tablets, crushed to a fine powder with a mortar and pestle, could be dissolved in water and then drawn into a syringe in preparation for potential IV injection → Xartemis XR became a gel-like substance
- IV vitro dose dumping
  - 75 ml simulated gastric fluid, with and without 80-proof vodka (1:1 with SGF). No dose dumping observed with Xartemis XR.

Correspondence Mallinckrodt Pharmaceuticals

Hysingla ER

- Extended-release hydrocodone with abuse deterrent characteristics
- HY (hydrocodone bitartrate)
- SING/SINGL (single entity)
- LA (long-acting)
- Available as 20, 30, 40, 60, 80, 100, 120 mg
  - “A proprietary extended-release solid oral dosage platform (RESISTEC) that uses a unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions.”
  - Deters chewing, injecting or snorting product

1 month supply:
- 20 mg - $255
- 120 mg - $1255
Abuse-deterrent formulations gets FDA nod

Original formulation was approved by the FDA for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which no alternative treatment options are adequate.

Abuse-deterrent technology – BeadTek – utilizes excipients that immediately form a viscous gel when crushed and dissolved in liquids or solvents

Will transition to new formulation in second quarter of 2015.
Zohydro® ER with BeadTek™

- Multi-particulate formulation of coated carrier beads in hard gelatin capsules
- Additional beads containing polyethylene oxide (inert)

BeadTek™ Technology

- PEO beads are inactive when used as indicated
- When crushed and dissolved in liquids or solvents, the PEO is designed to form a viscous gel

Shake for 10 min with water

1 mL water
Peripheral Opioid Antagonists

Block peripheral effects of opioids (mu antagonist) without crossing blood-brain barrier to reverse centrally mediated analgesia

- Methylnaltrexone (Relistor) - SC
- Alvimopan (Entereg) - PO
- Naloxegol (Movantik) - PO

Naloxegol (Movantik)

- Peglyated opioid antagonist (peripherally active mu opioid receptor antagonist – PAMORA)
- Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
Naloxegol (Movantik)

- First orally administered PAMORA for OIC
- Dosing
  - DC all maintenance laxative therapies (can resume after 3 days if suboptimal response to naloxegol)
  - 25 mg po qd 1 hour before or 2 hours after first meal of the day (take in AM)
  - May reduce to 12.5 mg if not tolerated, or if taken with 3A4 inhibitors
- Serious adverse effects-opioid withdrawal (1-3% patients)

Naloxegol (Movantik)

- Warnings/precautions
  - Risk of GI perforation in those with conditions associated with reduction in structural integrity of GI tract wall (e.g., PUD, diverticular disease, infiltrative GI tract malignancies, peritoneal mets)
  - Monitor for worsening GI pain; DC
  - Monitor for opioid withdrawal
- Adverse effects
  - Abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, hyperhidrosis
- $500/month (25 mg po qd)
**Naloxegol (Movantik)**

- 25 mg PO qday
- Time to peak effect <2 hours (second peak 0.5-4 hour after first peak)
- Watch out CYP3A4 drug interactions (dose adjust to 12.5 mg with mod CYP3A4 inhibitors)
- GFR < 60 mL/min: start with 12.5 mg
- Hasn’t been studied in severe liver impairment

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**Naloxone**

- Naloxone – semisynthetic derivative of thebaine, competitive antagonist at opioid receptors in the brain
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within
  - 1-2 minutes after IV administration
  - 2-5 minutes after IM or SC administration
- Half-life is 30-80 minutes; protective effect may wear off in 45 minutes after IV administration of a low dose
Naloxone

- **Dosing**
  - Naloxone hydrochloride 0.4 and 1 mg/ml solution for IV, IM or SC administration
  - Dose- 0.4-2 mg IV for adults
    - Can repeat every 2-3 minutes up to a total of 10 mg
  - Naloxone can be administered intranasally using a mucosal atomizer device
    - Syringe attached to a spray tip that fragments the medication into a fine mist
    - Dose is 2 mg (1 mg per nostril) which can be repeated in 3-5 minutes

Evzio (Naloxone)
Evzio (Naloxone)

- **Opioid antagonist for IM or SC injection** (0.4 mg/0.4 ml; prefilled autoinjector)
  - Electronic voice instruction system
- **Indicated for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression**
- **Dose**
  - < 1 year old: Pinch thigh muscle while administering; monitor injection site for residual needle parts
  - ≥ 1 year old: Inject IM or SC into the anterolateral aspect of thigh (through clothing ok)
  - May give additional doses every 2-3 minutes until desired response or emergency medical assistance available

Evzio (Naloxone)

- **Adverse reactions**
  - Post-op reversal of opioid depression: nausea, vomiting, sweating, tremulousness, tachycardia, hypotension, hypertension, seizures, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, cardiac arrest
  - Also, excessive naloxone doses in post-op: reversal of analgesia, agitation
Honorable Mention

- **Obredon (hydrocodone/guaifenesin)**
  - New combination antitussive/expectorant
  - Hydrocodone 2.5 mg and guaifenesin 200 mg/5 ml
  - 18 years and older for symptomatic relief of cough and to loosen mucus associated with the common cold

- **Dyloject (diclofenac sodium) Injection**
  - Management of mild to moderate pain in adults and for moderate to severe pain alone or in combination with opioids
  - 15-30 minutes to administer full dose
  - 37.5 or 50 mg in acute post-operative pain

Rescheduling

- Hydrocodone products rescheduled as CII
- Tramadol scheduled as CIV
  - “weaker” opioid
  - Dual mechanism analgesic
  - Lowers seizure threshold
  - Serotonin syndrome
  - Hypoglycemia
I’ll take the combo to go...

- Nortriptyline-morphine compared to each as monotherapy
- Patients randomized 1:1:1
  - Average baseline pain rating 5.3
  - Combination morphine + nortriptyline pain rating 2.6
  - Nortriptyline alone 3.1
  - Morphine alone 3.4
- Brief pain inventory scores lower for combination

Gilron I. Pain March 5, 2015

Acetaminophen Update

- Meta analysis – 13 randomized trials on low back pain or hip or knee osteoarthritis
- Results showed acetaminophen is ineffective in low back pain, and provides minimal short term benefit for osteoarthritis. (Machado GC et al. BMJ 2015;350:h1225)
Akynzeo (netupitant/palonosetron)

- Netupitant – selective antagonist of human substance P/neurokinin 1 (NK1) receptors (300 mg)
- Palonosetron – 5HT3 receptor antagonist (0.5 mg)
- Delayed emesis – largely associated with the activation of the tachykinin family NK1 receptors
  - Broadly distribute in the central and peripheral nervous systems
- Cisplatin-based chemotherapy regimens
- ~$500/capsule

Akynzeo (netupitant/palonosetron)

<table>
<thead>
<tr>
<th></th>
<th>Netupitant + palonosetron</th>
<th>Palonosetron</th>
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</thead>
<tbody>
<tr>
<td>Complete response (no emetic episode and no use of rescue medication for the 25-120 hour period)</td>
<td>90.4%</td>
<td>80.1%</td>
</tr>
<tr>
<td>Complete response to the 0-24 hours interval (acute phase)</td>
<td>98.5%</td>
<td>89.7%</td>
</tr>
<tr>
<td>Complete response within 120 hours (overall phase)</td>
<td>89.6%</td>
<td>76.5%</td>
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</tbody>
</table>

- 1 capsule about 1 hour prior to chemo with oral dexamethasone 12 mg given 30 minutes before chemo
- Dexamethasone 8 mg po daily on Days 2-4 (with cisplatin-based)
Belsomra (Suvorexant)

- Orexin antagonist indicated for insomnia characterized by difficulties with sleep onset and/or sleep maintenance.
- Orexin, also called hypocretin, is a neurotransmitter that regulates arousal, wakefulness and appetite.
- The orexin neuropeptide signaling system is a central promotor of wakefulness.
- Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R are thought to suppress wake drive.

Belsomra (Suvorexant)

- Denotes first approved within a pharmacologic drug class.
- Dose: 10 mg po taken no more than once per night and within 30 min of going to bed, with at least 7 hr remaining before the planned time of awakening.
- May increase to 20 mg; no benefit increasing to 30-40 mg po qd
  - 5 mg with 3A4 inhibitor (max 10 mg)
- Efficacy demonstrated objectively (polysomnography) and subjectively (patient reported sleep latency).
- $300/month
Belsomra (Suvorexant)

- **Adverse effect**
  - Somnolence, headache, dizziness, CNS depression
  - Daytime impairment, sleep paralysis, hallucinations
  - Complex sleep related behaviors (e.g., sleep-driving)

- **Monitoring**
  - Somnolence, CNS depression (DC with daytime somnolence)
  - Worsening insomnia or abnormal thinking and behavioral changes; complex sleep related behaviors
  - Suicidal ideations
  - Compromised respiratory function

- **Drug interactions** – alcohol, 3A4 inhibitors, CNS depressants

Goals of Medication Management in Advanced Illness

- **Provide quality care**
  - Select medications based on patient- and drug-related variables
  - Achieve the therapeutic goal
  - Prevent adverse effects

- **Conform to standards of practice**

- **Guided by evidence based when applicable**

- **Cost effective drug therapy**
  - Cost of medication and monitoring
Prescribing Continuum

- Drug therapy initiation
- Dosage titration
- Changing/adding drugs
- Switching or stopping drugs

The Process of Deprescribing

- Deprescribing – “the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life expectancy, values and preferences.”
- Positive, patient-centered intervention with inherent uncertainties
- Requires shared decision-making, informed patient consent and close monitoring of effects
  - The same as when starting medications
The Process of Deprescribing

1. Ascertain that all drugs the patient is currently taking and the reasons for each one.
2. Consider overall risk of drug-induce harm in individual patients in determining the required intensity of deprescribing intervention.
3. Assess each drug for its eligibility to be discontinued.
4. Prioritize drugs for discontinuation.
5. Implement and monitor drug discontinuation regimen.
Step 1

- Ascertain that all drugs the patient is currently taking and the reasons for each one.
- Defined by the Joint Commission as:
  - “The process of comparing a patient's medication orders to all of the medications that the patient has been taking. This reconciliation is done to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions. It should be done at every transition of care in which new medications are ordered or existing orders are rewritten. Transitions in care include changes in setting, service, practitioner or level of care.”

http://www.ihs.gov/ehr/index.cfm?module=medication_reconciliation

Scott et al. JAMA Internal Medicine 3-23-15

Step 2

- Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention.
Step 2

- Ascertain and assess risk according to:
  - Drug factors (number of drugs – single most important predictor)
  - Use of “high risk” drugs
    - Opioids, benzodiazepines, psychotropic drugs, NSAIDs, anticoagulants, digoxin, cardiovascular drugs, hypoglycemic agents, anticholinergic agents; NSAID + diuretic; ACE inhibitor and CKD
  - Patient factors
    - Age > 80 years old, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers, past or current nonadherence

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Step 3

- Assess each drug for its eligibility to be discontinued
  - No valid indication (drug use without indication)
  - Part of a prescribing cascade (drug-induced adverse effects)
  - Actual or potential harm of a drug > potential benefit (inappropriate drug therapy)
  - Disease and/or symptom control is ineffective or symptoms have completed resolved
  - Preventive drug is unlikely to confer any patient-important benefit over the patient’s remaining lifespan
  - Drugs are imposing unacceptable treatment burden (drug-induced adverse effects)

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MJ is a 74 year old man admitted to hospice with an admitting diagnosis of end-stage lung cancer. His prognosis is less than 2 months. He has no active comorbid conditions except hypothyroidism.

Which of the following medications would you feel comfortable stopping at this time?

A. Atorvastatin
B. Oral morphine long-acting tablets
C. Oral morphine solution
D. Senna
E. Levothyroxine

Drugs are rarely indicated if they do not confer a patient important outcome.
Un-useful Medications

- Unlikely to provide benefit
  - Medications for dementia in advanced disease
  - Riluzole for advanced ALS
  - Antimicrobial therapy

- Primary or secondary prevention
  - Dyslipidemia
  - Bisphosphonates

- Burden exceeds benefit
  - Anticoagulation

Step 4

- Prioritize drugs for discontinuation
- Deciding the order of discontinuation of drugs may depending on integrating 3 pragmatic criteria:
  - Those with the greater harm and least benefit
  - Those easiest to discontinue
    - Lowest likelihood of withdrawal reactions or disease rebound
  - Those that the patient is most willing to discontinue first
    - To gain buy-in to deprescribe other drugs
- Suggested approach is to rank drugs from high harm/low benefit to low harm/high benefit and discontinue the former in sequential order

Scott et al. JAMA Internal Medicine 3-23-15
Step 5

- **Implement and monitor drug discontinuation regimen**
- Explain and agree with patient/caregiver on management plan
- Cease 1 drug at a time so that harms (withdrawal reactions or return of disease) and benefits (resolution of adverse drug effects) can be attributed to specific drugs and rectified if necessary
- Wean patients off drugs more likely to cause adverse withdrawal effects, instruct patient/caregiver what to look for and report in the event of such effects occurring, and what actions they can self-initiate if these occur
- Communicate plan to all HCP; document reasons for and outcomes of deprescribing

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Mrs. D.

- Slim Caucasian 82 yo woman admitted to hospice with a diagnosis of Alzheimer’s disease (FAST 7D).
- Lives with daughter, primary caregiver.
- Daughter tells you Mom can be somewhat combative, particularly when she takes her medication
  - Patient frequently has dry heaves after daughter wrestles her into taking her meds
- Patient naps frequently during the day, doesn’t want to go to bed at night, or remain in bed during the night.
Mrs. D.

- Daughter gives the patient “Simply Sleep” (diphenhydramine 25 mg), two tablets at bedtime
  - Doesn’t seem to be helping
  - In fact, seems to make patient a bit more agitated
- Patient had a stroke 3 years ago with some left-sided weakness and residual physical discomfort.
- Patient has never had an MI, and she’s been taking alendronate for bone health for about 6 years.

Mrs. D’s Medication History

<table>
<thead>
<tr>
<th>Start date</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 years ago</td>
<td>Alendronate (Fosamax) 5 mg po once daily</td>
</tr>
<tr>
<td>4 years ago</td>
<td>Donepezil (Aricept) 23 mg once daily</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Methadone 2.5 mg po q12h</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Morphine oral solution, 5 mg po q2h prn additional pain</td>
</tr>
<tr>
<td></td>
<td>(uses one dose about three times a week)</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Senna, one or two tablets daily</td>
</tr>
<tr>
<td>3 years ago</td>
<td>Atorvastatin (Lipitor) 20 mg po qd</td>
</tr>
<tr>
<td>5 years ago</td>
<td>Multivitamin with iron daily</td>
</tr>
<tr>
<td>2 months ago</td>
<td>Simply Sleep (diphenhydramine 25 mg), 2 tablets at bedtime</td>
</tr>
</tbody>
</table>
Mrs. D.

- **Drug factors?**
  - Number of drugs
  - Use of “high risk” drugs
  - Past or current drug toxicity

- **Patient factors?**
  - Age > 80 years old
  - Cognitive impairment
  - Multiple comorbidities
  - Substance abuse
  - Multiple prescribers
  - Nonadherence

- **Medications:**
  - Alendronate 5 mg po qd
  - Donepezil 23 mg po qd
  - Methadone 2.5 mg po q12h
  - Morphine 5 mg po q2h prn
  - Senna, 1-2 tabs po qd
  - Atorvastatin 20 mg po qd
  - MVI po qd
  - Diphenhydramine 50 mg po qhs

Mrs. D.

- **Purpose for this med?**
- **How do you take this med?**
- **Taken regularly? Why not?**
- **Dx for med confirmed?**
- **Evidence of med effectiveness?**
- **Would benefit persist if DC?**
- **Used to treat adverse effect?**
- **Is this the BEST drug?**
- **Is this a “drug to avoid?”**
- **Is drug contraindicated?**

- **Drug causing side effects?**
- **Has drug “made a difference” and do you want to continue?**
- **Are you still having the troubling symptom?**
- **Is symptom mild or intermittent?**
- **Patient life expectancy? Drug benefit expectancy?**
- **Patient concerns re: med?**
- **Is taking the medication a burden for the patient?**
Mrs. D. – Prioritize Discontinuing Medications

1. Diphenhydramine
2. Donepezil
3. MVI
4. Alendronate
5. Atorvastatin
6. Senna
7. Morphine
8. Methadone

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